


Cite this: *RSC Adv.*, 2024, 14, 39543

Electrophilic aromatic substitution using fluorinated isoxazolines at the C5 position *via* C–F bond cleavage†

Kazuyuki Sato,^a Tomohiro Kuroki,^a Haruka Minami,^a Azusa Sato,^b Yukiko Karuo,^a Atsushi Tarui,^a Kentaro Kawai^a and Masaaki Omote^a

Electrophilic aromatic substitution at the C5 position of isoxazolines and construction of a new quaternary carbon center were achieved in this paper. This is the first report of carbon–carbon (C–C) bond formation onto isoxazoline without compromising the ring structure. Various aromatics including heteroaromatics gave the desired products in good yields, especially aromatics bearing electron-donating groups. The reaction proceeds *via* the S_EAr reaction mechanism, in which carbocation intermediates generated from the fluorinated isoxazolines *via* C–F bond cleavage reacted with aromatics.

Received 3rd October 2024
Accepted 11th December 2024

DOI: 10.1039/d4ra07102f

rsc.li/rsc-advances

Introduction

Heterocycles are important frameworks that are widely distributed in nature. The isoxazoline pharmacophore is one of the most important classes of five-membered nitrogen–oxygen containing heterocyclic compounds.¹ Acivicin is a fermentation product of *Streptomyces sviveus* and used as an effective inhibitor of γ -glutamyl transferase (Fig. 1).² Isoxadifen-ethyl is used as a herbicide safener that minimizes the effect of the herbicide, and can effectively alleviate a sulfonylurea herbicide ‘nic-sulfuron’ injury in maize.³ Roxifiban is a selective antagonist of the platelet glycoprotein IIb/IIIa receptor, which is the major receptor for fibrinogen on the platelet surface.⁴ Among such isoxazoline scaffolds, in particular, fluorinated or fluoroalkylated derivatives exhibit remarkable biological properties. For example, fluxametamide is an insecticide with a wide spectrum, and acts as an antagonist of GABA- and glutamate-gated chloride channels (GABA-Cl and Glu-Cl).⁵ Furthermore, CBM-301940 exhibited excellent *in vivo* PK/ADME properties and improved the cardiac efficiency in a rat heart global ischemia/reperfusion model.⁶

These scaffolds are commonly synthesized from fluorinated and/or fluoroalkylated building blocks which include classical reactions such as cycloaddition of nitrile oxide with alkene, condensation of diketone with hydroxylamine, and

cyclization of oxime (Fig. 2).⁷ However, both 4-fluorinated and 4-fluoroalkylated isoxazolines scaffolds have been little synthesized, especially isoxazolines bearing a quaternary carbon center at C5 position, which is important for the expression of biological activity. The Khisamutdinov group and the Shibata group succeeded in fluorination of isoxazolines bearing electron-withdrawing group at C4, respectively.⁸ These reactions afforded the corresponding 4-fluorinated products in good yields, but the formation of a new quaternary carbon center was not achieved owing to the use of starting substances that already have substituents at the C5 position (Scheme 1a and b). In 2020, an interesting fluoro-spirocyclization of isoxazoles was reported by Hamme and his co-workers.⁹ They also succeeded in the synthesis of 4-fluorinated isoxazolines, and achieved the construction of a new quaternary carbon center at C5 *via* C–O bond formation as well (Scheme 1c). To the best of our knowledge, there are only three reports regarding fluorine-containing isoxazolines at C4 position, although Houk *et al.* also reported the [3 + 2] cycloaddition of nitrile oxides to give the related isoxazoline system, but those were not main products.¹⁰

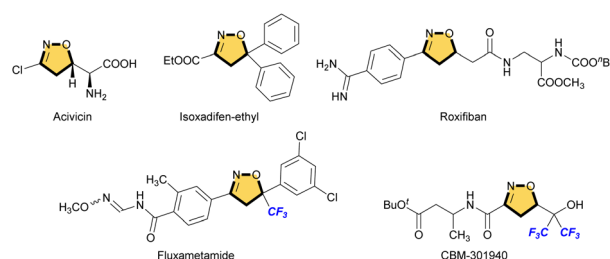


Fig. 1 Isoxazolines in bio-active compounds.

^aFaculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka, 573-0101, Japan. E-mail: sato@pharm.setsunan.ac.jp

^bSchool of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

† Electronic supplementary information (ESI) available. CCDC 2349492–2349494. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4ra07102f>



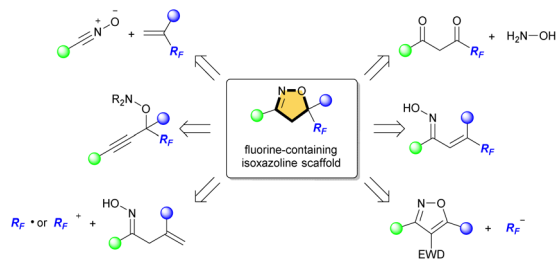
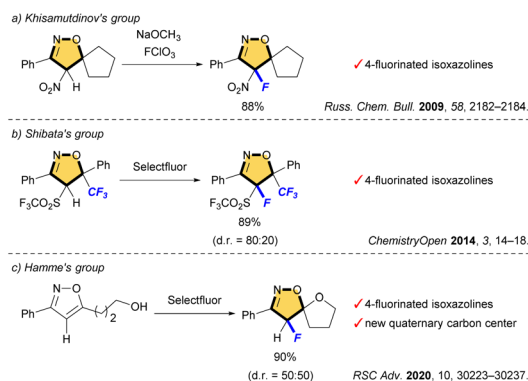


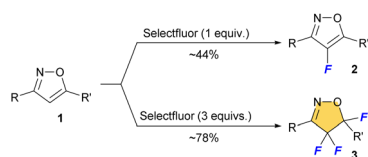
Fig. 2 Synthetic methods for fluorine-containing isoxazoles.

On the other hand, a carbon–fluorine (C–F) bond is one of the most stable chemical bonds, because it has the highest bond dissociation energies.¹¹ For this reason, transformations through stable C–F bond cleavage are difficult, but also challenging reactions. In recent years, several C–F bond cleavage reactions have been achieved by some groups, but there is still room in this field.¹² Based on such important background, we are interested in the construction of fluorinated isoxazoline system bearing a quaternary carbon center at C5 by using stable C–F bonds cleavage aimed at synthesizing a wide range of functional fluorinated 5-membered heterocyclic systems.

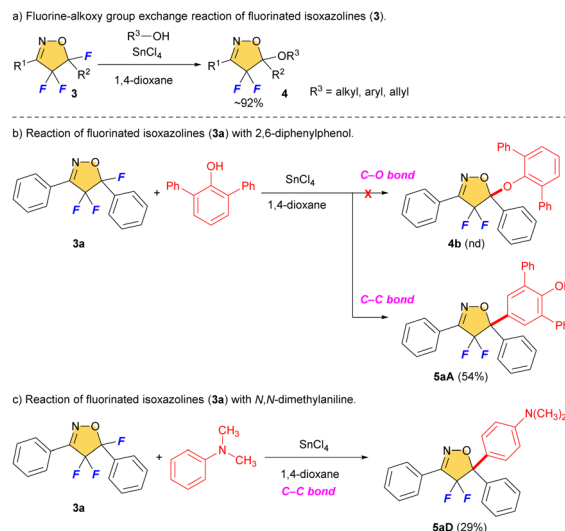
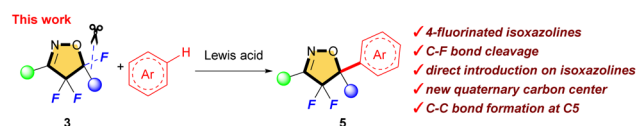
We reported selective fluorination of isoxazoles (1), which gave 4-fluorinated isoxazoles (2) or 4,4,5-trifluorinated isoxazoles (3) by using different amounts of Selectfluor, respectively (Scheme 2).¹³ Furthermore, when isoxazoles 3 and various alcohols were treated with SnCl₄, the corresponding 5-alkoxy-ylated products 4 were obtained in moderate to good yields (Scheme 3a).¹⁴ This reaction proceeds *via* an S_N1 type process along with C–F bond cleavage, and then C–O bond formation by



Scheme 1 Synthesis of 4-fluorinated isoxazoles bearing a quaternary carbon at C5.



Scheme 2 One-pot synthesis and selective fluorination of isoxazoles.

Scheme 3 Fluorine-alkoxy group exchange reaction of fluorinated isoxazoles and unexpected S_EAr products.Scheme 4 Direct introduction of carbon nucleophiles on fluorinated isoxazoles *via* C–F bond cleavage.

alcohol formed new quaternary carbon center at C5 position. In addition, this reaction could apply to other hetero atom nucleophiles such as thiols or amines to generate a new C–S or C–N bond at C5 position on starting isoxazoles.¹⁵ During the process of the synthesis of 4, sterically demanding phenol such as 2,6-diphenylphenol gave a novel aryl substituted product 5aA *via* electrophilic aromatic substitution (S_EAr) as shown in Scheme 3b.¹⁴ Furthermore, the reaction with *N,N*-dimethylaniline gave the similar C–C bond forming product 5aD that was introduced the aromatic ring directly at the C5 position of the isoxazoline scaffold, although the yield should be improved as shown in Scheme 3c. This is the first report for introducing carbon nucleophiles directly at the C5 position of the isoxazoline ring without compromising ring structure. In view of the results, we made the following hypothesis that the reaction of 3 with aromatic compounds might give various 4,4-difluoro-5-arylated isoxazoles (5) *via* S_EAr type processes which was directly constructed C–C bond at C5 position of isoxazoles (Scheme 4).

Results and discussion

For introducing an aromatic ring at the C5 position of isoxazoline 3a, we investigated the reaction conditions by using toluene as a carbon nucleophile. According to the previous result, we applied the best condition of the fluorine-alkoxy group exchange reaction as shown in entry 1 (Table 1).¹⁴



Table 1 Reaction conditions for S_EAr using toluene

Entry	Lewis acid	Solv. (mol L ⁻¹)	Temp (°C)	Yield ^a (%)		
				3a	4a	5aB
1	SnCl ₄	14-Dioxane (0.125)	Reflux	Trace	79	Trace
2	SnCl ₄	DCE (0.125)	Reflux	(34) ^b	47	—
3	SnCl ₄	THE (0.125)	Reflux	(23) ^b	(20) ^b	—
4	SnCl ₄	CH ₃ CN (0.125)	Reflux	—	57	18
5	SnCl ₄	DMF (0.125)	90	82	Trace	—
6	SnCl ₄	Sulfolane (0.125)	90	—	Trace	37
7	LiCl	Sulfolane (0.125)	90	96	—	—
8	BF ₃ ·Et ₂ O	Sulfolane (0.125)	90	—	—	58
9	TiCl ₄	Sulfolane (0.125)	90	—	19	—
10	FeCl ₃ ·6H ₂ O	Sulfolane (0.125)	90	—	61	—
11	SnCl ₂	Sulfolane (0.125)	90	—	98	—
12	YbCl ₃ ·6H ₂ O	Sulfolane (0.125)	90	—	94	—
13	BF ₃ ·Et ₂ O	Sulfolane (0.125)	90	—	—	66
14	BF ₃ ·Et ₂ O	Sulfolane (0.5)	90	—	—	27
15	BF ₃ ·Et ₂ O	Sulfolane (0.125)	120	—	—	12
16 ^c	BF ₃ ·Et ₂ O	Sulfolane (0.125)	90	—	—	64

^a Isolated yield. ^b The yield in parentheses was calculated by ¹⁹F NMR using PhCF₃ as an internal standard. ^c The reaction was carried out for 1 h.

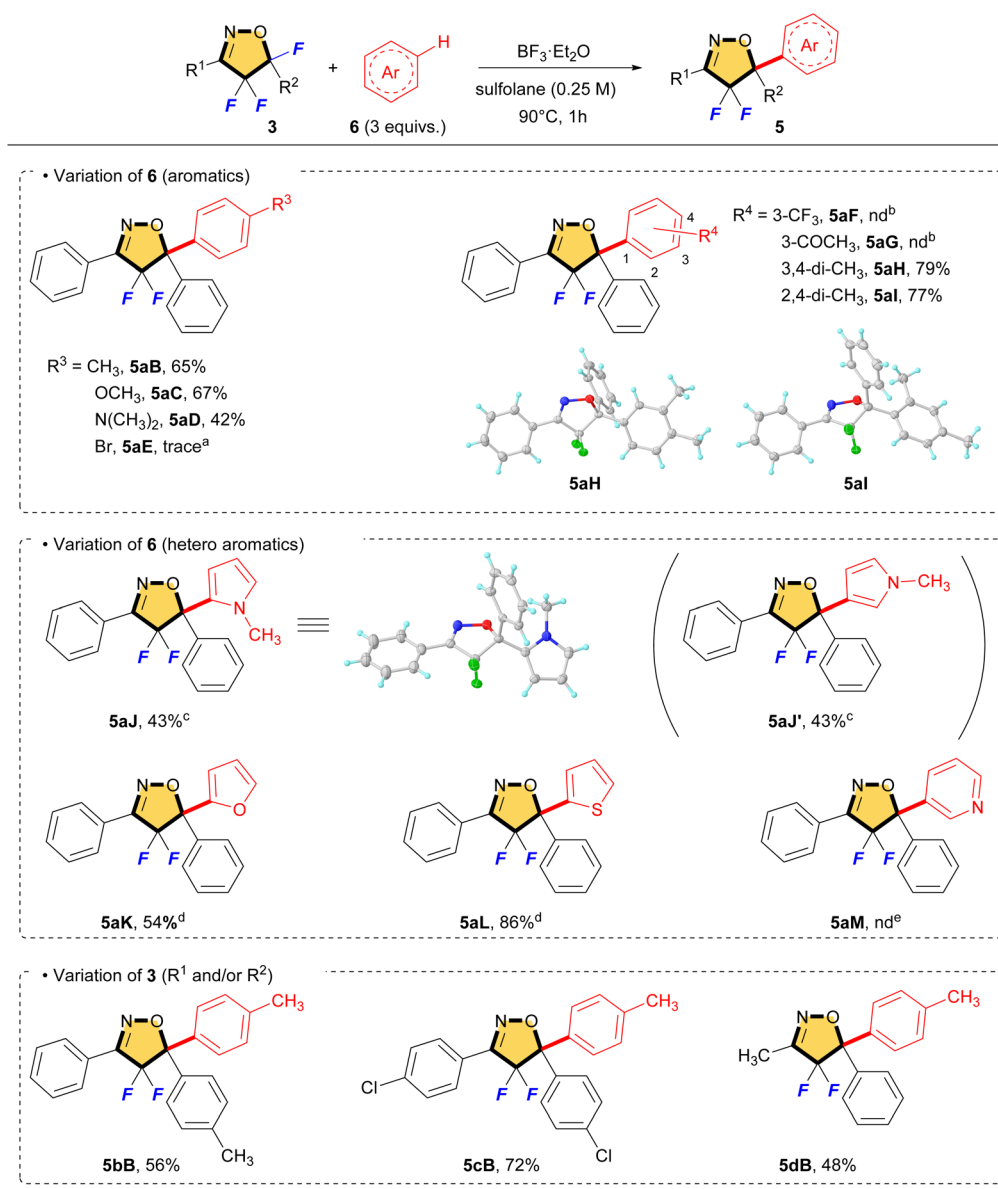
However, compound **5aB** was not obtained, but the main product is 5-hydroxylated compound **4a** in 79%. Therefore, various reaction solvents were examined. As shown in entries 4 and 6, acetonitrile and sulfolane gave the desired product **5aB**, and we found that sulfolane is the best solvent in this reaction. Next, various Lewis acids were examined. As shown in entry 7, using LiCl did not give the product at all, and only the starting material **3a** was recovered. On the other hand, using other Lewis acids such as YbCl₃, FeCl₃, SnCl₂ or TiCl₄ gave 5-hydroxylated product **4a**, although the **3a** was consumed as shown in entries 9–12. Based on these examinations, BF₃·Et₂O was the best Lewis acid and it gave the desired product **5aB** in 58% (entry 8). In further optimization of the reaction conditions, the solution concentrations and the temperature were investigated. In entry 13, increasing the solution concentration improved the yield of **5aB**. However, further high concentration or high reaction temperature greatly decreased the yield as shown in entries 14 and 15. On the other hand, the shortened reaction time did not affect the reaction yield (entry 16). So, we decided entry 16 is the best condition to give the desired product **5aB**.

On the basis of the optimized conditions, we explored the scope for this reaction, and the results are summarized in Table 2. The aromatics that are bearing on electron-donating groups proceeded smoothly to give the corresponding compounds (**5aB**–**5aD**, **5aH** and **5aI**) in moderate to good yields. On the other hand, the electron-deficient aromatics such as bromobenzene, benzonitrile and acetophenone did not

work well, but only 5-hydroxylated product **4a** was identified on ¹⁹F NMR. Heteroaromatic compounds could be applied to this reaction. Using *N*-methylpyrrole as the substrate, the desired compound **5aJ** was obtained in 43% together with its regioisomer **5aJ'** in 43% yield. Fortunately, these isomers (**5aJ** and **5aJ'**) were separable by column chromatography and the total yield of this reaction was 86%. With furan and thiophene, the reaction gave rise to the corresponding S_EAr products (**5aK** and **5aL**) including a small amount of their regioisomers in 54% and 86% yields. However, pyridine did not give the product at all, but the only starting material **3a** was recovered. Pyridine is a basic amine, so the formation of a BF₃ salt might be predominated during the reaction. Isoxazolines having substituted aromatics and alkyl group also reacted with toluene to give the corresponding products (**5bB**, **5cB**, and **5dB**). It is interesting that **5cB** involving chlorophenyl group at C5 could be obtained in a good yield by using the corresponding starting material, although the introduction of halobenzene *via* the S_EAr reaction failed (see **5aE**). As a side note, the molecular structures of **5aH**, **5aI** and **5aJ** were characterized by using single-crystal XRD analyses (**5aH** (CCDC: 2349494), **5aI** (CCDC: 2349492) and **5aJ** (CCDC: 2349493)).

We envisage that the reaction proceeds *via* S_EAr reaction mechanism (Fig. 3). The C–F bond of **3a** would be dissociated by Lewis acid and give the carbocation intermediate **A** (**Int A**). The stabilized **Int A** by the adjacent oxygen atom and/or benzene ring was trapped by the aromatics *via* S_EAr mechanism to give 5-arylated product **5** that bears a new quaternary carbon center.



Table 2 S_EAr reaction of 4,4,5-trifluorinated isoxazolines with aromatics via C–F bond cleavage

^a The product and the starting material (**3a**) were identified on ^{19}F NMR. ^b Only the 5-hydroxylated product (**4aA**) was identified on ^{19}F NMR.

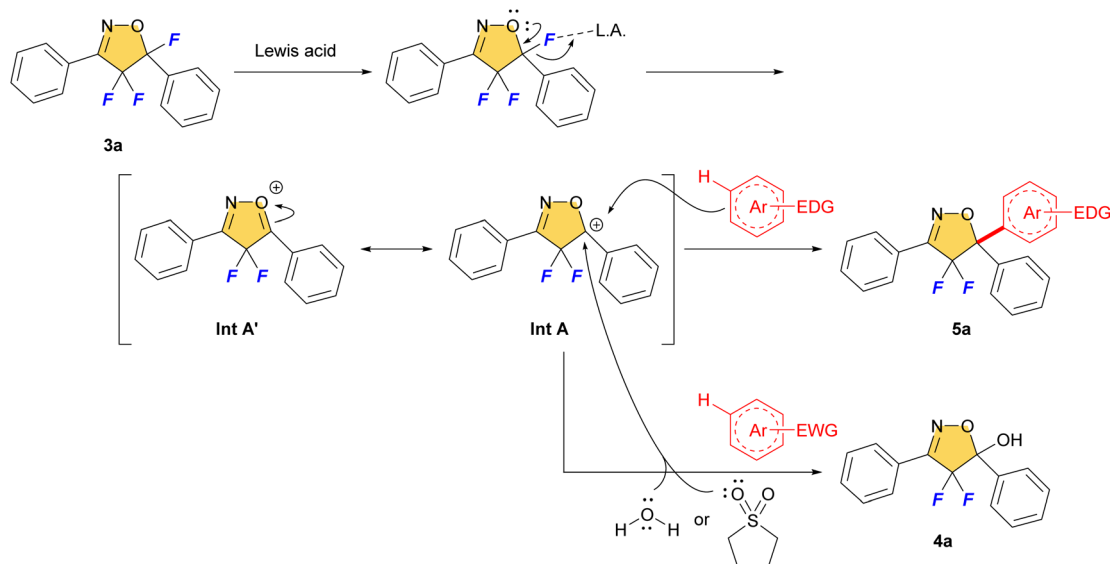
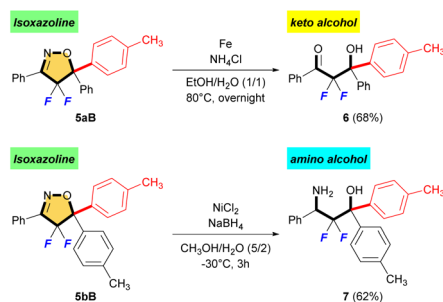
^c Separable regioisomer (**5aJ'**) was obtained in 43%. ^d Inseparable regioisomer was obtained in a small amount. ^e The starting material (**3a**) was recovered.

On the other hand, using poorly reactive electron-deficient aromatics preferentially led to the trapping of sulfolane and/or H_2O towards **Int A** to give 5-hydroxylated product **4a** reflecting the lower nucleophilicity of the aromatic substrate bearing an electron withdrawing substituent. So, it is important to use 'dry' solvent in this reaction.

In the last part, we explored several constructive reactions to demonstrate the synthetic utility of fluorinated isoxazoline products (Scheme 5). A reductive N–O bond cleavage of **5aB** followed by hydrolysis of imine to give α,α -difluoro- β -hydroxy

ketone **6** in 68% yield.¹⁶ Furthermore, treatment of **5bB** under reductive ring-opening condition by NaBH_4 and NiCl_2 afforded the corresponding α,α -difluoro- β -amino alcohol **7** in 62% yield.¹⁷ Interestingly, these are the first synthetic examples of α,α -difluoro- β -hydroxy ketone and α,α -difluoro- β -amino alcohol bearing two aromatic rings on the quaternary carbon center, although many syntheses of similar compounds using Reformatsky-type reaction and/or aldol-type reaction have been reported.¹⁸



Fig. 3 Proposed reaction mechanism of S_EAr reaction.

Scheme 5 The synthetic utility of fluorinated isoxazolines.

Conclusions

In conclusion, we succeeded in introducing various aromatic substituents at the C5 position of the fluorinated isoxazolines. Using the aromatics bearing electron-donating groups and heteroaromatics gave the desired products **5** in good yields. On the other hand, electron deficient aromatics did not give the products. The reaction would proceed *via* the S_EAr reaction mechanism, in which carbocation intermediates generated from the fluorinated isoxazolines *via* stable C–F bond cleavage reacted with aromatics. Isoxazoline is an important framework for bioactive compounds, and we expect that these products also have interesting activities.

Data availability

All experimental procedures and additional data can be found in the ESI.†

Author contributions

KS wrote the manuscript. KS and MO conceived and designed the experiments. KS, TK and HM performed the experiments

and analyzed the data. AS carried out the single-crystal XRD analyses. All authors discussed the results and reviewed the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Dr Haruhiko Fukaya at Tokyo University of Pharmacy and Life Sciences for support with X-ray crystallographic studies.

Notes and references

- (a) K. A. Kumar, M. Govindaraju, N. Renuka and G. V. Kumar, Isoxazolines: An insight to their synthesis and diverse applications, *Int. J. Res. Pharm. Chem.*, 2015, **7**, 250–257; (b) N. Agrawal and P. Mishra, The synthetic and therapeutic expedition of isoxazole and its analogs, *Med. Chem. Res.*, 2018, **27**, 1309–1344; (c) G. Kumar and R. Shankar, 2-Isoxazolines: A Synthetic and Medicinal Overview, *ChemMedChem*, 2021, **16**, 430–447; (d) I. L. Gonçalves, G. Machado das Neves, L. P. Kagami, V. L. Eifler-Lima and A. A. Merlo, Discovery, development, chemical diversity and design of isoxazoline-based insecticides, *Bioorg. Med. Chem.*, 2021, **30**, 115934; (e) D. Feng, S. Wu, B. Jiang, S. He, Y. Luo, F. Li, B. Song and R. Song, Discovery of novel isoxazoline derivatives containing diaryl ether against fall armyworms, *J. Agric. Food Chem.*, 2023, **71**, 6859–6870; (f) S. Huang, H. Ma, Z. Wang, P. Zhang, S. Li, Y. Li, A. Liu, Y. Li and Q. Wang, Design, synthesis, and insecticidal and fungicidal activities of ether/oxime-ether containing

- isoxazoline derivatives, *J. Agric. Food Chem.*, 2023, **71**, 5107–5116.
- 2 L. Allen, R. Meck and A. Yunis, The inhibition of gamma-glutamyl transpeptidase from human pancreatic carcinoma cells by (alpha S,5S)-alpha-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (AT-125; NSC-163501), *Res. Commun. Chem. Pathol. Pharmacol.*, 1980, **27**, 175–182.
 - 3 (a) H. Ahrens, G. Lange, T. Müller, C. Rosinger, L. Willms and A. van Almsick, 4-Hydroxyphenylpyruvate dioxygenase inhibitors in combination with safeners: Solutions for modern and sustainable agriculture, *Angew. Chem. Int. Ed. Engl.*, 2013, **52**, 9388–9398; (b) L. Sun, R. Wu, W. Su, Z. Gao and C. Lu, Physiological basis for isoxadifen-ethyl induction of nicosulfuron detoxification in maize hybrids, *PLoS One*, 2017, **12**, e0173502.
 - 4 (a) C.-B. Xue, J. Wityak, T. M. Sielecki, D. J. Pinto, D. G. Batt, G. A. Cain, M. Sworin, A. L. Rockwell, J. J. Roderick, S. Wang, M. J. Orwat, W. E. Fietze, L. L. Bostrom, J. Liu, C. A. Higley, F. W. Rankin, A. E. Tobin, G. Emmett, G. K. Lalka, J. Y. Sze, S. V. DiMeo, S. A. Mousa, M. J. Thoolen, A. L. Racanelli, E. A. Hausner, T. M. Reilly, W. F. DeGrado, R. R. Wexler and R. E. Olson, Discovery of an orally active series of isoxazoline glycoprotein IIb/IIIa antagonists, *J. Med. Chem.*, 1997, **40**, 2064–2084; (b) C.-B. Xue and S. A. Mousa, DMP 754, *Drugs Future*, 1998, **23**, 707–711.
 - 5 M. Asahi, M. Kobayashi, T. Kagami, K. Nakahira, Y. Furukawa and Y. Ozoe, Fluxametamide: A novel isoxazoline insecticide that acts via distinctive antagonism of insect ligand-gated chloride channels, *Pestic. Biochem. Physiol.*, 2018, **151**, 67–72.
 - 6 J.-F. Cheng, Y. Huang, R. Penuliar, M. Nishimoto, L. Liu, T. Arrhenius, G. Yang, E. O'Leary, M. Barbosa, R. Barr, J. R. B. Dyck, G. D. Lopaschuk and A. M. Nadzan, Discovery of potent and orally available malonyl-CoA decarboxylase inhibitors as cardioprotective agents, *J. Med. Chem.*, 2006, **49**, 4055–4058.
 - 7 (a) K. Matoba, H. Kawai, T. Furukawa, A. Kusuda, E. Tokunaga, S. Nakamura, M. Shir and N. Shibata, Enantioselective synthesis of trifluoromethyl-substituted 2-isoxazolines: Asymmetric hydroxylamine/enone cascade reaction, *Angew. Chem., Int. Ed.*, 2010, **49**, 5762–5766; (b) H. Kawai, K. Tachi, E. Tokunaga, M. Shiro and N. Shibata, Trifluoromethylation of aromatic isoxazoles: Regio- and diastereoselective route to 5-trifluoromethyl-2-isoxazolines, *Angew. Chem., Int. Ed.*, 2011, **50**, 7803–7806; (c) V. Kumar and K. Kaur, Fluorinated isoxazolines and isoxazoles: A synthetic perspective, *J. Fluorine Chem.*, 2015, **180**, 55–97; (d) J. Zhao, M. Jiang and J.-T. Liu, Synthesis of fluoromethyl-substituted isoxazolines via transition metal-free oxyfluorination of alkenyl oximes, *Adv. Synth. Catal.*, 2017, **359**, 1626–1630; (e) N. Umemoto, A. Imayoshi and K. Tsubaki, Nitrile oxide cycloaddition reactions of alkenes or alkynes and nitroalkanes substituted with O-alkyloxime groups convertible to various functional groups, *Tetrahedron Lett.*, 2020, **61**, 152213; (f) A. Sperga, A. Kazia and J. Veliks, Monofluorinated 5-membered rings via fluoromethylene transfer: synthesis of monofluorinated isoxazoline N-oxides, *Org. Biomol. Chem.*, 2021, **19**, 2688–2691; (g) W. Riley, A. C. Jones, K. Singh, D. L. Browne and A. M. Stuart, Accessing novel fluorinated heterocycles with the hypervalent fluoriodane reagent by solution and mechanochemical synthesis, *Chem. Commun.*, 2021, **57**, 7406–7409; (h) M. Yang, W. Shao, L. Zuo, J. Wang, Y. Xu, G. Mao and G.-J. Deng, Site-selective radical trifluoromethylaminooxylation of olefins for the modular synthesis of diverse β -trifluoromethyl trisubstituted hydroxylamines and beyond, *Org. Lett.*, 2023, **25**, 2728–2732.
 - 8 (a) G. Kh. Khisamutdinov, V. Okhlobystina and A. A. Fainzil'berg, Fluorination of 4-nitroisoxazoline salts. Synthesis of 4-fluoro-4-nitroisoxazolines and 4-fluoroisoxazoles, *Russ. Chem. Bull.*, 2009, **58**, 2182–2184; (b) H. Kawai, Y. Sugita, E. Tokunaga, H. Sato, M. Shiro and N. Shibata, Diastereoselective additive trifluoromethylation/halogenation of isoxazole triflones: Synthesis of all-carbon-functionalized trifluoromethyl isoxazoline triflones, *Open Chem.*, 2014, **3**, 14–18.
 - 9 P. Das, S. Boone, D. Mitra, L. Turner, R. Tandon, D. Raucher and A. T. Hamme II, Synthesis and biological evaluation of fluoro-substituted spiro-isoxazolines as potential anti-viral and anti-cancer agents, *RSC Adv.*, 2020, **10**, 30223–30237.
 - 10 (a) Y.-M. Chang, J. Sims and K. N. Houk, Mechanisms of 1,3-dipolar cycloadditions to highly electron-deficient dipolarophiles, *Tetrahedron Lett.*, 1975, **16**, 4445–4448; (b) M. Prakesch, D. Grée, R. Grée, J. Carter, I. Washington and K. N. Houk, Stereoselectivity of nitrile oxide cycloadditions to chiral allylic fluorides: Experiment and theory, *Chem.-Eur. J.*, 2003, **9**, 5664–5672.
 - 11 Y. G. Lazarou, A. V. Prosmits, V. C. Papadimitriou and P. Papagiannakopoulos, Theoretical calculation of bond dissociation energies and enthalpies of formation for halogenated molecules, *J. Phys. Chem. A*, 2001, **105**, 6729–6742.
 - 12 (a) T. Niwa, H. Ochiai, Y. Watanabe and T. Hosoya, Ni/Cu-Catalyzed defluoroborylation of fluoroarenes for diverse C–F bond functionalizations, *J. Am. Chem. Soc.*, 2015, **137**, 14313–14318; (b) T. Iwasaki, K. Yamashita, H. Kuniyasu and N. Kambe, Co-Catalyzed cross-coupling reaction of alkyl fluorides with alkyl Grignard reagents, *Org. Lett.*, 2017, **19**, 3691–3694; (c) N. Sugihara, K. Suzuki, Y. Nishimoto and M. Yasuda, Photoredox-catalyzed C–F bond allylation of perfluoroalkylarenes at the benzylic position, *J. Am. Chem. Soc.*, 2021, **143**, 9308–9313; (d) F. Wang, Y. Nishimoto and M. Yasuda, Insertion of diazo esters into C–F bonds toward diastereoselective one-carbon elongation of benzylic fluorides: Unprecedented BF₃ catalysis with C–F bond cleavage and re-formation, *J. Am. Chem. Soc.*, 2021, **143**, 20616–20621; (e) J. Zhou, B. Jiang, Y. Fujihira, Z. Zhao, T. Imai and N. Shibata, Catalyst-free carbosilylation of alkenes using silyl boronates and organic fluorides via selective C–F bond activation, *Nat. Commun.*, 2021, **12**, 3749; (f) T. Ma, X.-P. Wei, X.-C. Wang, X.-X. Qiao, G. Li, Y. He and X.-J. Zhao, Highly enantioselective synthesis of 3a-fluorofuro[3,2-b]indolines via



- organocatalytic aza-Friedel–Crafts reaction/selective C–F bond activation, *Org. Lett.*, 2023, **25**, 8666–8671.
- 13 K. Sato, G. Sandford, K. Shimizu, S. Akiyama, M. J. Lancashire, D. S. Yufit, A. Tarui, M. Omote, I. Kumadaki, S. Harusawa and A. Ando, Synthesis of fluorinated isoxazoles using Selectfluor™: preparation and characterization of 4-fluoroisoxazole, 4,4,5-trifluoroisoxazoline and 4,4-difluoro-5-hydroxyisoxazoline systems from one-pot and multi-step processes, *Tetrahedron*, 2016, **72**, 1690–1698.
 - 14 K. Sato, G. Sandford, Y. Konishi, N. Yanada, C. Toda, A. Tarui and M. Omote, Lewis acid promoted fluorine-alkoxy group exchange reactions for the synthesis of 5-alkoxy-4,4-difluoroisoxazoline systems, *Org. Biomol. Chem.*, 2019, **17**, 2818–2823.
 - 15 K. Sato, K. Nakano, T. Ueda, Y. Kitamura, Y. Tanaka, Y. Karuo, A. Tarui, K. Kawai and M. Omote, Construction of new quaternary carbon center of fluorinated isoxazolines at C5 position via C–F bond cleavage, *J. Fluorine Chem.*, 2024, **279**, 110335.
 - 16 L. Wang, K. Zhang, Y. Wang, W. Li, M. Chen and J. Zhang, Enantioselective synthesis of isoxazolines enabled by palladium-catalyzed carboetherification of alkenyl oximes, *Angew. Chem., Int. Ed.*, 2020, **59**, 4421–4427.
 - 17 X.-T. Li, Q.-S. Gu, X.-Y. Dong, X. Meng and X.-Y. Liu, A copper catalyst with a cinchona-alkaloid-based sulfonamide ligand for asymmetric radical oxytrifluoromethylation of alkenyl oximes, *Angew. Chem., Int. Ed.*, 2018, **57**, 7668–7672.
 - 18 (a) S. Sasaki, T. Suzuki, T. Uchiya, S. Toyota, A. Hirano, M. Tanemura, H. Teramoto, T. Yamauchi and K. Higashiyama, Synthesis of α,α -difluoro- β -hydroxy ketone via the La(OTf)₃-catalyzed aldol reaction of carbonyl compounds with difluoroenol *O*-Boc esters, *J. Fluorine Chem.*, 2016, **192**, 78–85; (b) A. Tarui, M. Oduti, S. Shinya, K. Sato and M. Omote, Decarboxylative aldol reaction of α,α -difluoro- β -ketocarboxylate salt: a facile method for generation of difluoroenolate, *RSC Adv.*, 2018, **8**, 20568–20575; (c) X.-S. Hu, P.-G. Ding, J.-S. Yu and J. Zhou, A Sc(OTf)₃ catalyzed Mukaiyama–Mannich reaction of difluoroenoxy silanes with unactivated ketimines, *Org. Chem. Front.*, 2019, **6**, 2500–2505; (d) Z. Ni, R. Sun, J. Wu, C. Xu, J. Huang and F. Wu, Indium-mediated 1,2-addition of iododifluoromethyl ketones with α,β -unsaturated ketones, *Tetrahedron*, 2022, **119**, 132855; (e) R. Sun, X. Lian, J. Huang, J. Wu, Y. Li, Z. Chen, Z. Qu, L. Song and F. Wu, Iron-mediated Reformatsky reaction of iododifluoromethyl ketones with aldehydes: Preparation of α,α -difluoro- β -hydroxyketone derivatives, *J. Fluorine Chem.*, 2023, **269**, 110151; (f) F. Livernaux, S. Lavieville, P. Guiffrey, J.-M. Campagne and E. Leclerc, Enantioselective aldol reaction with difluoroenoxy silanes catalyzed by cationic palladium aqua complexes, *Eur. J. Org. Chem.*, 2023, **26**, e202300467.

